

REMARKS

Before addressing the Office Action, Applicants thank the Examiner for her comments in both the Office Action and the subsequent interview.

Claims 1-49 constitute the pending claims in the present application. Claims 12 to 19, 31 to 47 and 49 have been withdrawn from consideration. Claims 1 to 10, 20 to 29 and 48 stand rejected. Claims 11 and 30 are objected to as being dependent on a rejected base claim.

Claims 1 to 11, 20 to 30 and 48 have been amended. Amendment of the originally filed claims should in no way be construed as an acquiescence, narrowing, or surrender of any subject matter. The amendments are being made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application. Applicants reserve the option to prosecute further the originally filed claims or similar ones, in the instant or a subsequent patent application.

Support for these amendments may be found throughout the written description, the Figures and the originally filed claims. No new matter has been added. Without limitation, support for the claim amendments may be found at: originally filed claims 3 and 4 to 10; Formulas 16, 23, 31, 34, 35, 36, 37, 38 and 40 of Figure 1; Figure 8; Formula 48 of Figure 9; Formula 57 of Figure 11; page 13, line 1, to page 19, line 11; page 21, lines 6 to 15; page 31, lines 15 to 16; page 33, lines 16 to 22; page 34, line 19, to page 35, line 10; page 36, lines 1 to 5; page 36, line 21, to page 38, line 8; and Examples 3, 7, 8, 9 and 11.

Without limitation, described below in more detail is support for each of the claim amendments made:

- For Amended Claims 1, 20 and 48: Amendments to Formulas 1, 2 and 3, Z2 and D.

In amended claim 1, two new formulas, Formulas II and III were specified. In addition, Z2 has been modified from the originally filed claim 1 and D has been specified. Applicants have added these two formulas, and made these other amendments, to address the objections made by the Examiner in paragraph 4(g) of the Office Action, concerning the use of “tautomer” and “isomeric form.” As described in detail in the application at page 30, last full paragraph, to

page 31, with the three structures for fluorescein, fluorescein itself can take either a “Free acid” or “Lactone” form (in addition to the “Zwitterion” depicted there). Originally filed claim 1 described this portion of the claimed fluorescein-based ligand using “Z2”, and then specified Z2 as being “N, HOOCCH₂CH₂C-, HOOC-CH=CH-C-, (2-carboxyphenyl)-C-, (2-sulfophenyl)-C-, (2-carboxy-3,4,5,6-tetrachlorophenyl)-C-, (2-carboxy-4-nitrophenyl)-C-, (2-carboxy-5-nitrophenyl)-C-, (2-carboxy-4-aminophenyl)-C-, (2-carboxy-5-aminophenyl)-C-, (2,4-dicarboxyphenyl)-C-, (2,5-dicarboxyphenyl)-C-, (2,4,5-tricarboxyphenyl)-C-, or other substituted (2-carboxyphenyl)-C- derivative.”

Applicants have amended Z2 to specify a number of the forms of Z2 that the claimed fluorescein-based ligand may have, all of which were taught in the application as originally filed. Thus, in amended claim 1, Formula I refers to that embodiment in which Z2 is either not capable of forming the “Lactone” structure on page 31 of the application (e.g., when Z2 is N, as specified in the originally filed claim 1), or the case when Z2 is in the “Free acid” form, so that although the particular embodiment may be able to form the “Lactone,” the claimed fluorescein-based ligand is not that tautomer but instead the Free Acid tautomer (e.g., HOOCCH₂CH₂C-, also as specified in the originally filed claim 1).

Further, in amended claim 1, Z2 now provides that the phenyl portion may be substituted with E, support for which is found in the application with Formula 2B on page 32 in which the phenyl portion is there shown optionally substituted with K. Please note that in amended claim 1, Applicants have used E for this optional substitution of the phenyl ring of Z2 (also identified as the phenyl ring formed by carbons 3 to 8 of the structure depicted on page 30 of the application) to distinguish that optional substitution from the optional substitution with K of two other phenyl rings of the claimed fluorescein-based ligand (also identified as the phenyl rings formed in part by carbons 1' to 8' of the structure depicted on page 30 of the application). Applicants have done so to allow dependent claims to be made in which the substitution of those three phenyl rings vary, as described below. The application as originally filed contemplated independent substitution of these various phenyl rings, as indicated at for example page 32, fifth line from the bottom of the page, in referring to Formula 2B (“each K, independently, may be ...” (emphasis added)). Further, Z2 of the originally filed claim 1 specified examples of such substitution with E as now claimed, with for example “(2,4,5-tricarboxyphenyl)-C-” etc.

Also for Z2 in amended claim 1, the hydrogen atoms of “HOOCCH₂CH₂C-, HOOC-CH=CH-C-” are “optionally substituted” and “said carbonyls” (including the 2-carboxy of (2-carboxyphenyl)-C and the 2-sulfo of (2-sulfophenyl)-C-) are optionally a “carbonyl other than carboxylic acid.” Such substitutions are known to those of skill in the art and are generally taught by the application at the carry-over paragraph from page 22 to page 23. In particular, such variations are contemplated for the hydrogen atoms in the application at page 13, the third full paragraph, and page 14, the first full paragraph, which teaches that hydrogen atoms of alkyl and alkenyl groups like those in “HOOCCH₂CH₂C-” or HOOC-CH=CH-C-” may be substituted. Further, such variations for carbonyls in particular are described at page 17 of the application, second full paragraph.

Formula II of amended claim 1 presents the claimed fluorescein-based ligand in the “Lactone” tautomeric form, with the optional substitution with E of the indicated phenyl ring as described above.

Finally, Formula III of amended claim 1 presents the case when the Z2 described above is “HOOCCH₂CH₂C-, HOOC-CH=CH-C-”, but instead of being in the “Free acid” form, the embodiment is in the “Lactone” form. To claim this “Lactone” form, D along with the remainder of the lactone structure set forth in Formula III has been specified and is consistent with the embodiments taught by Z2 of originally filed claim 1, optionally substituted as described above.

- For Amended Claims 1, 20 and 48: Amendment to A.

Support for the amendment to A in amended claim 1 is found, for example, at the first full paragraph of page 32 of the application and from originally filed claim 2. “-C(H)=” has been included in A, with support at, for example, Formulas 5 and 6 of the application at page 37.

- For Amended Claims 1, 20 and 48: Amendment to K and E.

Support for the amendment to K in amended claim 1 is found, for example, at the carry-over paragraph of page 32 to page 33 of the application and from originally filed claim 3. Further, E has been included in amended claim 1 for the reason described above, and support for E is found in the application as indicated above for K and also in Formula 2B on page 32 of the

application, which shows the phenyl ring optionally substituted (also identified as the phenyl ring formed by carbons 3 to 8 of the structure depicted on page 30 of the application).

- For Amended Claims 1, 20 and 48: Amendment to V.

In general, on pages 33 to 38, the application teaches that a large range of possible Lewis bases are contemplated for V (emphasis added): “In general, V contains a Lewis base fragment that is contemplated to encompass numerous chemical moieties having a variety of structural, chemical and other characteristics capable of forming coordination bonds with a metal ion. The types of functional groups capable of forming coordinate complexes with metal ions are too numerous to categorize here, and are known to those of skill in the art. For example, such moieties will generally include functional groups capable of interaction with a metal center, e.g., *heteroatoms such as nitrogen, oxygen, sulfur, and phosphorus.*” Thus, the application expressly contemplates including as part of V various Lewis bases to form, for example, a variety of chelating agents as part of the claimed fluorescein-based ligand.

In particular, support for the amendment to V in amended claim 1 that is directed to “(i) at least three Lewis bases that are capable of forming a tridentate chelating agent, wherein at least one of said three Lewis bases is a ring heteroatom of a heterocyclic group” is found in numerous locations throughout the application. At page 33, the third full paragraph, the application expressly contemplates that V may contain sufficient Lewis bases to give a tridentate (or greater) chelating agent (emphasis added): “Alternatively, V itself includes two or more atoms that serve as Lewis bases and are *capable of forming bidentate, tridentate, tetradentate or greater chelating agents* by themselves or in conjunction with the oxygen atoms of the hydroxyl substituents of the fluorescein structure. In certain embodiments, the atoms that serve to donate electrons for V are nitrogen, oxygen, sulfur or phosphorus.”

Further, the application lists “heterocyclic” as one of the Lewis base functionalities contemplated for V at the end of the carry-over paragraph on page 35: “... and heterocyclic compounds, including pyridine and the like.” “Heterocyclic group” is defined on pages 14 and 15 of the application in part as being a ring structure that includes heteroatom(s), and the application expressly indicates that the Lewis base in V may be a heteroatom, as quoted above.

Finally, there are numerous examples in the application that fall within the scope of this claimed V, including for example all of the following Formulas: 3, 4, 16, 31, 32 to 40 and 47. In addition, the first formula of originally filed claim 11 is also an example of this V.

In particular, support for the amendment to V in amended claim 1 that is directed to “a secondary nitrogen atom doubly bonded to a carbon atom of A to form an imine, wherein said secondary nitrogen atom is capable of forming a bidentate chelating agent with the oxygen atom of OZ or Q” is found at numerous locations throughout the application. That V may include an “imine” is expressly stated in the last paragraph on page 35 of the application and in describing Formulas 5 and 6 on page 37 of the application.

Further, in the first sentence of the third full paragraph on page 33, the application expressly states that the Lewis base of V may be capable of forming at least a bidentate chelating agent with the oxygen atom of the claimed fluorescein-based ligand: “In certain embodiments, V is capable of forming a bidentate chelating agent consisting of an atom of V donating an electron pair and the oxygen atom of the adjacent hydroxyl group(s) of the fluorescein ring structure.” This is further expressly considered when describing the imine on page 37: “In certain embodiments, R1 may include a further one or more atoms that may serve as a Lewis base and for a chelating agent with the nitrogen of the NR1 moiety and optionally the hydroxyl of the aromatic ring.”

Finally, there are numerous examples in the application that fall within the scope of this claimed V, including for example all of the following Formulas: 4, 5, 23, 47 and the compound prepared in Figure 8. In addition, the second formula of originally filed claim 11 is also an example of this V.

For the claims that depend from independent claims 1 and 20, we identify here exemplary additional support for the amendments made (as appropriate):

- For Amended Claims 2 and 21: Many formulas in the application, including, for example, Formulas 1B and 2B, show Y and Q equal to O. Further, A is oftentimes depicted as -CH₂-, optionally substituted.

- For Amended Claims 3 and 22: At page 33, second full paragraph, of the application, K is expressly indicated as being halogen. Further, for originally filed claim 1, the substitution of the phenyl ring that now corresponds to E included halogen, amino, carbonyl and nitro.

- For Amended Claims 4 and 23: At page 32 of the application, the second and third full paragraphs describes halogen substitution at the 2' and/or 7' positions with K. The second full paragraph on page 33 further describes K as halogen.

- For Amended Claims 5 and 24: As stated above for V, nitrogen donor atoms are contemplated Lewis bases, and further, in describing V on pages 34 to 36 and in the definition of "heterocyclic group" on pages 14 and 15, exemplary heterocycles containing nitrogen ring atoms are described.

- For Amended Claims 6 and 25: At page 33, in the third full paragraph, the application expressly contemplates when V comprises at least three Lewis bases that are capable of forming a tetradentate ligand "with the oxygen atoms of the hydroxyl substituents of the fluorescein structure."

- For Amended Claims 7 and 26: See comment above for amended claims 4 and 23.
- For Amended Claims 8 and 27: See comment above for amended claims 3 and 22.
- For Amended Claims 9 and 28: See comment above for amended claims 4 and 23.
- For Amended Claims 10 and 29: See comment above for amended claims 3 and 22.
- For Amended Claims 11 and 30: See comment above for amended claims 4 and 23 regarding K.

Rejections under 35 U.S.C. § 112, Second Paragraph

To expedite prosecution among other reasons, Applicants have amended certain of the pending claims to address points 2, 3 and 4 of the outstanding Office Action.

In brief and without limitation, Applicants note that additional structures have been added to independent claims 1, 20 and 48 in part to address the various tautomer/isomers that are possible with the claimed fluorescein based-ligands and diagnostic kits. As indicated above, there is support in the application and originally filed claims for the claim amendments made.

In particular, with respect to the rejections specified by the Examiner in paragraph 4 of the Office Action:

- 4(a): The variable A has been amended as described above.
- 4(b): The variable K has been amended as described above.
- 4(c): This error has been corrected by amendment.
- 4(d): The claim language identified by the Examiner has been deleted by amendment.
- 4(e): The claim language identified by the Examiner has been deleted by amendment.
- 4(f): Claim 4 has been amended, so Applicants respectfully submit that this rejection is no longer applicable.
- 4(g): Claims 4 and 8 have been amended, so Applicants respectfully submit that this rejection is no longer applicable.
- 4(h): Claims 5 and 24 have been amended, so Applicants respectfully submit that this rejection is no longer applicable.
- 4(i): Claim 9 has been amended, so Applicants respectfully submit that this rejection is no longer applicable.

Accordingly, Applicants respectfully request reconsideration and withdrawal of these rejections.

Rejections under 35 U.S.C. § 102(a)/(b)

To expedite prosecution among other reasons, Applicants have amended certain of the pending claims to address points 6, 7 and 8 of the outstanding Office Action.

In brief and without limitation, Applicants note that V in independent claims 1, 20 and 48 has been amended to comprise certain types of Lewis bases, including in part a “ring atom of a heterocyclic group” and an “imine”, and further to require that the claimed V be capable of forming the tridentate or bidentate chelating agent specified in the claims. Applicants respectfully submit that none of the compounds identified in the outstanding Office Action anticipates nor renders obvious the amended claims. As indicated above, there is support in the description and originally filed claims for the claim amendments made.

In particular, with respect to the rejections specified by the Examiner in paragraphs 7 and 8 of the Office Action:

- Shipchandler et al: Formulas 2b and 2c do not indicate or suggest a “ring atom of a heterocyclic group” or an “imine”.
- Kaplan et al: Formula II of Figure 1 does not indicate or suggest a “ring atom of a heterocyclic group” or an “imine”.
- Werts et al: Formulas 3 and 4 of Scheme 1 do not indicate or suggest a “ring atom of a heterocyclic group” or an “imine”.
- AKSO NOBEL: The formulas on page 15, lines 9-10, do not indicate or suggest a “ring atom of a heterocyclic group” or an “imine”.
- Fiechtner et al: The first formula of column 13 does not indicate or suggest a “ring atom of a heterocyclic group” or an “imine”.
- Jackson: the first structure of column 25 does not indicate or suggest a “ring atom of a heterocyclic group” or an “imine”.

- ABBOT (EP 297,303): The description at page 4, lines 1 to 31, does not indicate or suggest an “imine”, nor does it indicate or suggest a molecule in which there are at least three Lewis bases that are capable of forming a tridentate chelating agent, wherein at least one of said three Lewis bases is a ring atom of a heterocyclic group.

- Kirkemo et al: The formula at column 3, lines 20-39, does not indicate or suggest a “ring atom of a heterocyclic group” or an “imine”.

- ABBOT (EP 201,751): Applicants respectively note that the Examiner’s reference to “col. 4, lines 7-14” for this reference was unclear to Applicants, because the copy of the reference provided with the Office Action has pages, not columns. Nonetheless, Applicants have reviewed this reference, and none of Examples I to VI in that reference indicate or suggest an “imine”, nor do any of them indicate or suggest a molecule in which there are at least three Lewis bases that are capable of forming a tridentate chelating agent, wherein at least one of said three Lewis bases is a ring atom of a heterocyclic group.

- Ghosal et al: The formulas 2 and 3 of Figure 1 do not indicate or suggest a “ring atom of a heterocyclic group” or an “imine”.

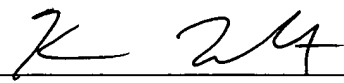
Accordingly, Applicants respectfully request reconsideration and withdrawal of these rejections.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-832-1000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this application be charged to **Deposit Account No. 06-1448**.

Respectfully Submitted,

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